IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Tsuyoshi NAGANUMA et al

Application No.: 10/538,514 Confirmation No.: 1878

Filed: June 9, 2005 Group Art Unit: 4133

For: SOLID DRUG FOR ORAL USE

Examiner: Walter E. Webb

DECLARATION UNDER 37 C.F.R 1.132

Honorable Commissioner for Patents

Washington, D.C. 20231

Sir:

I, Tsuyoshi NAGANUMA of 4622-38, Toyoshina, Azumino-shi, Nagano 399-8205 JAPAN, being duly sworn, declare and state:

THAT I am by profession a research chemist having a bachelor's degree in industrial chemistry from Chuo University in March 1990.

THAT I have been employed since April 1990 by Kissei Pharmaceutical Co., Ltd. of 19-48, Yoshino, Matsumoto-shi, Nagano 399-8710 JAPAN and engaged in engineering and research mainly on:

production on drug products in the production department of the same company from April 1990 to September 1990; and then

formulation technology studies on drug products in Central Research Laboratories of the same company from October 1990 up to now.

THAT I am one of co-inventors of the invention disclosed in the above-identified U.S. patent application and hence I am fully familiar therewith.

In order to demonstarate that the present invention is unobvious over Salpekar (US4,757,090) and Shar (US5,370,878), we have conducted the following experiment for comparing the capsule of the present invention with a capsule prepared from the compositions suggested by Salpekar and Shar.

Experiment

1. Preparation of comparative capsule 1A, 1B, 2A and 2B

Comparative capsule 1A and 1B

In order to compare the dissolution rate of the capsule of the present invention with a formulation suggested by Salpekar, we have prepared a capsule using KMD-3213 instead of acetaminophen, partially pregelatinized starch (Starch 1500), povidone and stearic acid acoording to the composition of Example 1 as described in Salpekar (US4,757,090) as follows.

A mixture of KMD-3213 (9.0 g), partially pregelatinized starch (0.85 g) and povidone (0.1 g) was mixed sufficiently. The mixture was granulated with water. The granule was dried using a Static Solid bed drier at an inlet air temperature of about 70 °C for 2 hours, and sieved. Stearic acid (0.05 g) was added to the sieved granules and mixed for 1 minute, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213 (1A).

Furthermore, sodium lauryl sulfate (0.05 g) was added to the lubricated granules containing stearic acid and mixed for 1

minute, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213 (1B).

Comparative capsule 2A and 2B

In order to compare the dissolution rate of the capsule of the present invention with a formulation suggested by Shar, we have prepared a capsule using KMD-3213 instead of acetaminophen, partially pregelatinized starch (Starch 1500), povidone (K-90), croscarmellose sodium (Ac-Di-Sol), stearic acid and colloidal sillicon dioxide acoording to the composition of Example 1 as described in Shar (US5,370,878) as follows.

A mixture of KMD-3213 (9.0 g), partially pregelatinized starch (0.35 g), croscarmellose sodium (0.2 g) and povidone (0.2 g) was mixed sufficiently. The mixture was granulated with water. The granule was dried using a Static Solid bed drier at an inlet air temperature of about 70 °C for 2 hours, and sieved. Colloidal sillicon dioxide (0.05 g) and stearic acid (0.2 g) were added to the sieved granules and mixed for 1 minute, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213 (2A).

Furthermore, sodium lauryl sulfate (0.2 g) was added to the lubricated granules containing stearic acid and colloidal sillicon dioxide and mixed for 1 minute, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213 (2B).

2. Dissolution test

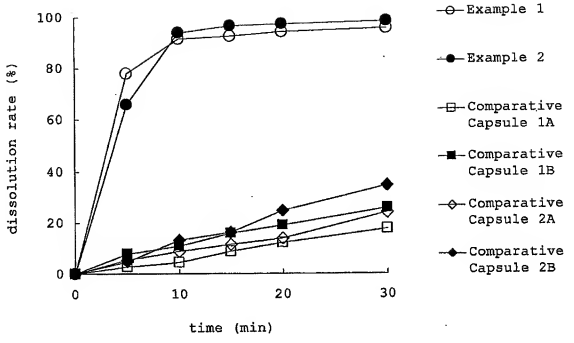
In accordance with the procedures of "Dissolution Test Method" as described in Test example 4 in the present specification, the capsules of example 1 and 2 of the present

invention; and the comparative capsules 1A, 1B, 2A and 2B as prepared above were tested. Their dissolution rates are shown in Drawing 1.

Table 1

Capsule	Capsule of the present invention		Comparative Capsule			
	Example 1	Example 2	1A	1B	2A	2B
KMD-3213	2.0	4.0	90.0	90.0	90.0	90.0
D-Mannitol	134.4	132.4				
Partially pregelatinized starch (PCS)	26.0	26.0				
Partially pregelatinized starch (Starch 1500)	9.0	9.0	8.5	8.5	3.5	3.5
Corn starch						
Croscarmellose Sodium (Ac-Di-Sol)					2.0	2.0
Povidone (K-30)			1.0	1.0		
Povidone (K-90)					2.0	2.0
Magnesium stearate	1.8	1.8				
Sodium Lauryl Sulfate	1.8	1.8		0.5		2.0
Stearic acid			0.5	0.5	2.0	2.0
Colloidal Sillicon Dioxide					0.5	0.5
total weight	175.0	175.0	100.0	100.5	100.0	102.0

Drawing 1



The results of dissolution tests show clearly that the capsules of the present invention have much higher dissolution rate as compared with those of the comparative capsule 1A, 1B, 2A and 2B. Such advantageous effects of the capsule of the present invention cannot be predicted from the teaching of Salpekar and Shar.

Therefore, we believe that the capsule of the present invention is unobvious over Salpekar and Shar.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

November 21, 2008

Tsuyoshi Naganuma

Tsuyoshi NAGANUMA